

# SEQUENCE LISTING

<110> Tang, Jordan J.N.  
Hong, Lin  
Ghosh, Arun K.

<120> Inhibitors of Memapsin 2 and Use Thereof

<130> OMRF 182

<140> Not Yet Assigned

<141> 2000-06-27

<150> 60/141,363

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<150> 60/210,292

<151> 2000-06-08

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<170> PatentIn Ver. 2.1

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<212> DNA

<213> Homo sapiens

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<211> 488

<212> PRT

<213> Homo sapiens

<220>

<223> Purified Memapsin 2

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<223> Amino Acids 28-48 are remnant putative propeptide residues

<220>

<223> Amino Acids 58-61, 78, 80, 82-83, 116, 118-121, 156, 166, 174, 246, 274, 276, 278-281, 283, and 376-377 are residues in contact with the OM99-2 inhibitor

<220>

<223> Amino acids 54-57, 61-68, 73-80, 86-89, 109-111, 113-118, 123-134, 143-154, 165-168, 198-202, and 220-224 are N-lobe Beta Strands

<220>

<223> Amino Acids 184-191 and 210-217 are N-lobe Helices

<220>

<223> Amino acids 237-240, 247-249, 251-256, 259-260, 273-275, 282-285, 316-318, 331-336, 342-348, 354-357, 366-370, 372-375, 380-383, 390-395, 400-405, and 418-420 are C-lobe Beta Strands

<220>

<223> Amino Acids 286-299, 307-310, 350-353, 384-387, and 427-431 are C-lobe Helices

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Ala Gly Val Leu Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro  
1 5 10 15

Leu Arg Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg  
20 25 30

Glu Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val  
35 40 45

Glu Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val  
50 55 60

Glu Met Thr Val Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp  
 65 70 75 80

Thr Gly Ser Ser Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu  
 85 90 95

His Arg Tyr Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg  
 100 105 110

Lys Gly Val Tyr Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu  
 115 120 125

Gly Thr Asp Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg  
 130 135 140

Ala Asn Ile Ala Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly  
 145 150 155 160

Ser Asn Trp Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg  
 165 170 175

Pro Asp Asp Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr  
 180 185 190

His Val Pro Asn Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro  
 195 200 205

Leu Asn Gln Ser Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile  
 210 215 220

Gly Gly Ile Asp His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro  
 225 230 235 240

Ile Arg Arg Glu Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile  
 245 250 255

Asn Gly Gln Asp Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys  
 260 265 270

Ser Ile Val Asp Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val  
 275 280 285

Phe Glu Ala Ala Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys  
 290 295 300

Phe Pro Asp Gly Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala  
 305 310 315 320

Gly Thr Thr Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met  
 325 330 335

Gly Glu Val Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln  
 340 345 350

Tyr Leu Arg Pro Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr  
 355 360 365

Lys Phe Ala Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val  
 370 375 380

Ile Met Glu Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile  
 385 390 395 400

Gly Phe Ala Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala  
 405 410 415

Ala Val Glu Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr  
 420 425 430

Asn Ile Pro Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val  
 435 440 445

Met Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val  
 450 455 460

Cys Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe  
 465 470 475 480

Ala Asp Asp Ile Ser Leu Leu Lys  
 485

<210> 3  
 <211> 503  
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 <223> Pro-memapsin 2

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 <223> Amino Acids 1-15 are vector-derived residues

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 <223> Amino Acids 16-64 are a putative pro peptide

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<223> Amino Acids 1-13 are the T7 promoter

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<223> Amino Acids 16-456 are Pro-memapsin 2-T1

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<223> Amino Acids 16-421 are Promemapsin 2-T2

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1 5 10 15

Gly Val Leu Pro Ala His Gly Thr Gln His Gly Ile Arg Leu Pro Leu  
20 25 30

Arg Ser Gly Leu Gly Gly Ala Pro Leu Gly Leu Arg Leu Pro Arg Glu  
35 40 45

Thr Asp Glu Glu Pro Glu Glu Pro Gly Arg Arg Gly Ser Phe Val Glu  
50 55 60

Met Val Asp Asn Leu Arg Gly Lys Ser Gly Gln Gly Tyr Tyr Val Glu  
65 70 75 80

Met Thr Val Gly Ser Pro Pro Gln Thr Leu Asn Ile Leu Val Asp Thr  
85 90 95

Gly Ser Ser Asn Phe Ala Val Gly Ala Ala Pro His Pro Phe Leu His  
100 105 110

Arg Tyr Tyr Gln Arg Gln Leu Ser Ser Thr Tyr Arg Asp Leu Arg Lys  
115 120 125

Gly Val Tyr Val Pro Tyr Thr Gln Gly Lys Trp Glu Gly Glu Leu Gly  
130 135 140

Thr Asp Leu Val Ser Ile Pro His Gly Pro Asn Val Thr Val Arg Ala  
145 150 155 160

Asn Ile Ala Ala Ile Thr Glu Ser Asp Lys Phe Phe Ile Asn Gly Ser  
165 170 175

Asn Trp Glu Gly Ile Leu Gly Leu Ala Tyr Ala Glu Ile Ala Arg Pro  
180 185 190

Asp Asp Ser Leu Glu Pro Phe Phe Asp Ser Leu Val Lys Gln Thr His  
195 200 205

Val Pro Asn Leu Phe Ser Leu Gln Leu Cys Gly Ala Gly Phe Pro Leu  
 210 215 220

Asn Gln Ser Glu Val Leu Ala Ser Val Gly Gly Ser Met Ile Ile Gly  
 225 230 235 240

Gly Ile Asp His Ser Leu Tyr Thr Gly Ser Leu Trp Tyr Thr Pro Ile  
 245 250 255

Arg Arg Glu Trp Tyr Tyr Glu Val Ile Ile Val Arg Val Glu Ile Asn  
 260 265 270

Gly Gln Asp Leu Lys Met Asp Cys Lys Glu Tyr Asn Tyr Asp Lys Ser  
 275 280 285

Ile Val Asp Ser Gly Thr Thr Asn Leu Arg Leu Pro Lys Lys Val Phe  
 290 295 300

Glu Ala Ala Val Lys Ser Ile Lys Ala Ala Ser Ser Thr Glu Lys Phe  
 305 310 315 320

Pro Asp Gly Phe Trp Leu Gly Glu Gln Leu Val Cys Trp Gln Ala Gly  
 325 330 335

Thr Thr Pro Trp Asn Ile Phe Pro Val Ile Ser Leu Tyr Leu Met Gly  
 340 345 350

Glu Val Thr Asn Gln Ser Phe Arg Ile Thr Ile Leu Pro Gln Gln Tyr  
 355 360 365

Leu Arg Pro Val Glu Asp Val Ala Thr Ser Gln Asp Asp Cys Tyr Lys  
 370 375 380

Phe Ala Ile Ser Gln Ser Ser Thr Gly Thr Val Met Gly Ala Val Ile  
 385 390 395 400

Met Glu Gly Phe Tyr Val Val Phe Asp Arg Ala Arg Lys Arg Ile Gly  
 405 410 415

Phe Ala Val Ser Ala Cys His Val His Asp Glu Phe Arg Thr Ala Ala  
 420 425 430

Val Glu Gly Pro Phe Val Thr Leu Asp Met Glu Asp Cys Gly Tyr Asn  
 435 440 445

Ile Pro Gln Thr Asp Glu Ser Thr Leu Met Thr Ile Ala Tyr Val Met  
 450 455 460

Ala Ala Ile Cys Ala Leu Phe Met Leu Pro Leu Cys Leu Met Val Cys  
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Gln Trp Arg Cys Leu Arg Cys Leu Arg Gln Gln His Asp Asp Phe Ala  
485 490 495

Asp Asp Ile Ser Leu Leu Lys  
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<210> 4  
<211> 10  
<212> PRT  
<213> Artificial Sequence

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<223> Description of Artificial Sequence: Primer

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<210> 5  
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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic  
Peptide

<400> 5  
Ser Glu Val Asn Leu Asp Ala Glu Phe Arg  
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<210> 6  
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<212> PRT  
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Peptide

<400> 6



Ser Val Asn Met Ala Glu Gly Asp

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5

<210> 7

<211> 12

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic  
Peptide

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Lys Gly Gly Val Val Ile Ala Thr Val Ile Val Lys

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<210> 8

<211> 4

<212> PRT

<213> Homo sapiens

<400> 8

Asp Thr Ser Gly

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<210> 9

<211> 8

<212> PRT

<213> Homo sapiens

<400> 9

Leu Val Asn Met Ala Glu Gly Asp

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<210> 10

<211> 28

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Primer

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<210> 11  
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<212> DNA  
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<220>  
<223> Description of Artificial Sequence: Primer

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gacgttgggg ccatggggga tgcttacc

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<210> 12  
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<212> DNA  
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<210> 13  
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<212> DNA  
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<223> Description of Artificial Sequence: Primer

<400> 13  
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<210> 14  
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<223> Description of Artificial Sequence: Primer

<400> 14  
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<210> 15  
<211> 23  
<212> DNA  
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<223> Description of Artificial Sequence: Primer

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23

<210> 16  
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<212> DNA  
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<220>  
<223> Description of Artificial Sequence: Primer

<400> 16  
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<210> 17  
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<212> DNA  
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<220>  
<223> Description of Artificial Sequence: Primer

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<210> 18  
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<212> DNA  
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<223> Description of Artificial Sequence: Primer

<400> 18  
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22

<210> 19  
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<212> DNA  
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<400> 19  
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<210> 21  
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<212> DNA  
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<223> Description of Artificial Sequence: Primer

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<220>  
<223> Description of Artificial Sequence: Oxidized  
Insulin B-chain

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<223> Xaa at site 3 represents cysteic acid

<400> 22

His Leu Xaa Gly Ser His Leu Val

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5

<210> 23

<211> 8

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Oxidized  
Insulin B-chain

<220>

<223> Xaa at site 1 represents cysteic acid

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Xaa Gly Glu Arg Gly Phe Phe Tyr

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<210> 24

<211> 5

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic  
Peptide

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Val Gly Ser Gly Val

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<210> 25

<211> 7

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic  
Peptide

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Val Gly Ser Gly Val Leu Leu  
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<210> 26  
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Peptide

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<210> 27  
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<220>  
<223> Description of Artificial Sequence: Inhibitors

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Val Asn Leu Ala Ala Glu Phe  
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<210> 28  
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<223> Description of Artificial Sequence: Inhibitors

<400> 28  
Glu Val Asn Leu Ala Ala Glu Phe  
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<210> 29  
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<223> Description of Artificial Sequence: Synthetic Peptide

<400> 29

Asn Leu Ala Ala

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<210> 30

<211> 10

<212> PRT

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<223> Description of Artificial Sequence: Synthetic Peptide

<400> 30

Val Gly Ser Gly Val Leu Leu Ser Arg Lys

1

5

10

<210> 31

<211> 326

<212> PRT

<213> Homo sapiens

<220>

<223> Amino acids 2-5, 6-9, 13-20, 25-32, 65-67, 69-74, 79-87, 89-91, 99-106, 119-122, 150-154, 164-167, 180-183, 191-194, 196-199, 201-204, 210-214, 221-223, 258-262, 265-269, and 275-278 are Beta Strands

<220>

<223> Amino acids 281-284, 286-288, 298-301, 310-315, and 319-324 are Beta strands

<220>

<223> Amino acids 48-51, 111-114, 136-142, 225-234, 249-254, 271-274, and 303-306 are Helices

<220>

<223> Amino acids 12-13, 30, 32, 34-35, 73-77, 111, 117, 120, 189, 213, 215, 217-220, 287, 289, 291, 298, and 300 are residues in contact with pepstatin.

<220>

<223> Pepsin

<400> 31

Val Asp Glu Gln Pro Leu Glu Asn Tyr Leu Asp Met Glu Tyr Phe Gly  
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20 25 30

Thr Gly Ser Ser Asn Leu Trp Val Pro Ser Val Tyr Cys Ser Ser Leu  
35 40 45

Ala Cys Thr Asn His Asn Arg Phe Asn Pro Glu Asp Ser Ser Thr Tyr  
50 55 60

Gln Ser Thr Ser Glu Thr Val Ser Ile Thr Tyr Gly Thr Gly Ser Met  
65 70 75 80

Thr Gly Ile Leu Gly Tyr Asp Thr Val Gln Val Gly Gly Ile Ser Asp  
85 90 95

Thr Asn Gln Ile Phe Gly Leu Ser Glu Thr Glu Pro Gly Ser Phe Leu  
100 105 110

Tyr Tyr Ala Pro Phe Asp Gly Ile Leu Gly Leu Ala Tyr Pro Ser Ile  
115 120 125

Ser Ser Ser Gly Ala Thr Pro Val Phe Asp Asn Ile Trp Asn Gln Gly  
130 135 140

Leu Val Ser Gln Asp Leu Phe Ser Val Tyr Leu Ser Ala Asp Asp Gln  
145 150 155 160

Ser Gly Ser Val Val Ile Phe Gly Gly Ile Asp Ser Ser Tyr Tyr Thr  
165 170 175

Gly Ser Leu Asn Trp Val Pro Val Thr Val Glu Gly Tyr Trp Gln Ile  
180 185 190

Thr Val Asp Ser Ile Thr Met Asn Gly Glu Ala Ile Ala Cys Ala Glu  
195 200 205

Gly Cys Gln Ala Ile Val Asp Thr Gly Thr Ser Leu Leu Thr Gly Pro  
210 215 220

Thr Ser Pro Ile Ala Asn Ile Gln Ser Asp Ile Gly Ala Ser Glu Asn



225		230		235		240
Ser Asp Gly Asp Met Val Val Ser Cys Ser Ala Ile Ser Ser Leu Pro						
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Asp Ile Val Phe Thr Ile Asn Gly Val Gln Tyr Pro Val Pro Pro Ser						
	260		265		270	
Ala Tyr Ile Leu Gln Ser Glu Gly Ser Cys Ile Ser Gly Phe Gln Gly						
	275		280		285	
Met Asn Leu Pro Thr Glu Ser Gly Glu Leu Trp Ile Leu Gly Asp Val						
	290		295		300	
Phe Ile Arg Gln Tyr Phe Thr Val Phe Asp Arg Ala Asn Asn Gln Val						
305		310		315		320
Gly Leu Ala Pro Val Ala						
	325					